II. REMARKS

Preliminary Remarks

Claims 23 and 24 are amended and new claims 27-36 are added.

Claims 23 and 24 are amended to incorporate the subject matter of original claims 10 and 14. New claims 27-31 are dependent on claim 23 and new claims 32-36 are dependent on claim 24. Claims 27-31 and 32-36 specify the subject matter of original claims 11-13, 16, and 17, respectively.

Patentability Remarks

35 U.S.C. §112, First Paragraph, for lack of written description

Claims 23 and 24 were rejected under 35 U.S.C. §112, First Paragraph, as allegedly containing subject matter that is not described in the specification in a way that would convey that the inventor had possession of the claimed invention at the time of filing. The official action stated that there is insufficient written description of the chimeric protein, "particularly with respect to the antibody element in the absence of an antigen specificity...."

Claims 23 and 24 were further rejected under 35 U.S.C. §112, First Paragraph, because the specification allegedly does not provide sufficient biochemical information, *e.g.*, sequence information or identification of antibody-producing hybridomas, to distinctly identify the antigen-binding portion of the chimeric protein.

Claims 23 and 24 are both amended to be directed to methods wherein the chimeric protein that is administered is one comprising an antibody fragment that comprises at least the variable region binding domain of an antibody that specifically binds an antigen expressed by a tumor or cancer cell. Support for this functional feature of the chimeric protein is described in the specification, *e.g.*, at page 18, lines 17-20. The applicants submit that one of skill in the art would regard the invention of the amended claims as one that is distinctly identified by the claims and described by the specification in a way that would convey that the inventors had possession of the claimed invention at the time of filing. Withdrawal of the rejection of the claims under 35 U.S.C. §112, First Paragraph, for lack of written description is therefore respectfully requested.

35 U.S.C. §112, Second Paragraph,

Claims 23 and 24 were rejected under 35 U.S.C. §112, Second Paragraph, as being indefinite for the following reasons:

(a) claims 23 and 24 depended on withdrawn claim 10;

(b) the phrase "treating a disease in a patient in need of such treatment" in claim 24 allegedly did not inform one of skill in the art of the metes and bounds of the claim.

Claims 23 and 24 are amended so that they are not dependent on withdrawn claim 10; and claim 24 is further amended to be directed to "a method of treating a tumor or cancer in a patient in need of such treatment." The applicants submit that one of skill in the art would be familiar with the end points of cancer treatment and would recognize the metes and bounds of the claimed methods. Withdrawal of the rejection of the claims under 35 U.S.C. §112, Second Paragraph, is therefore respectfully requested.

35 U.S.C. §103(a)

Claims 23 and 24 were rejected under 35 U.S.C. 103(a) as being obvious in view of Whitlow et al. (U.S. Patent No. 5,767,260) and/or Denny et al. (U.S. Patent No. 5,872,334), in view of Grabstein et al. (U.S. Patent No. 5,747,024), further in view of Armitage et al. (U.S. Patent No. 6,290,972).

The applicants respectfully traverse the rejection of the claims as allegedly being obvious in view of the cited references.

Claims 23 and 24 are both directed to therapeutic methods comprising administering comprising a chimeric protein comprising at its amino terminus at least one antibody fragment that comprises at least the variable region binding domain of an antibody that specifically binds an antigen expressed by a tumor or cancer cell, and further comprising at its carboxy terminus the extracellular binding portion of CD40 ligand.

Whitlow et al. describes an antigen-binding fusion protein comprising an immunoeffector or cytolytic polypeptide attached to the C terminus of an antigen-binding polypeptide that binds to a tumor cell (see columns 9 and 10). However, the reference does

not describe or suggest making or using a tumor antigen-binding fusion protein wherein the attached immunoeffector is a CD40 ligand.

Grabstein et al. provides a general teaching to use CD40 ligand as a vaccine adjuvant, and describes CD40 ligand as an immunoeffector.

Denny et al. describes a multivalent vaccine composition for eliciting an immune response against an immune cell tumor (*e.g.*, lymphoma or leukemia) that comprises recombinant variable regions of two or more different immunoglobulins produced by the immune cell tumor. In the invention described by Denny et al., recombinant variable regions of tumor-associated immunoglobulins are used as antigens for eliciting an immune response against the tumor cells. Denny et al. also teaches that in order to enhance the immune response against the tumor cells, the antigenic recombinant Ig variable regions can be linked to an immune-enhancing cytokine (see column 3, lines 29-62). While Denny et al. describes an antigenic fusion protein comprising an immunoglobulin variable region produced by a tumor cell, it does not describe a fusion protein that comprises an immunoglobulin variable region that binds specifically to a tumor cell.

Armitage et al. (U.S. Patent No. 6,290,972) discloses nucleotide and amino acid sequences for murine and human CD40 ligand and states that CD40 ligand may be useful as a vaccine adjuvant (see the paragraph bridging columns 10-11).

Individually or collectively, none of the cited references describes or suggests a therapeutic method comprising administering an anti-tumor composition comprising CD40 ligand as an immunoeffector or adjuvant. The official action takes the position that it would have been obvious for one of skill in the art to make a fusion protein comprising the extracellular binding portion of CD40 ligand attached to the C terminus of a tumor antigen-binding polypeptide, given that Whitlow et al. described making and using a fusion protein comprising an immunoeffector attached to the C terminus of a tumor antigen-binding polypeptide, and Grabstein et al. and Armitage et al. taught that CD40L can be used as a vaccine adjuvant (*i.e.*, is an immunoeffector).

The applicants traverse the view that the claimed invention would have been obvious in view of the combination of cited references, because **at the time of filing, the prior art clearly taught away from administering an agonist of CD40 such as the extracellular binding portion of CD40 ligand in an anti-cancer composition.**

For example, Biancone et al. (J. Immunol., 1999, 163:6201-6208, copy attached) reported that *in vitro*, soluble CD40 ligand stimulates the motility of both CD40-bearing tumor cells and endothelial cells (see Figs. 2 and 4). Endothelial cell motility is known to be positively correlated with efficient vascularization. Biancone et al. also showed that tumor vascularization *in vivo* is significantly stimulated by the binding of a CD40 agonist such as CD40 ligand to CD40 (see Fig. 7 and the discussion on page 6206). In addition, Biancone et al. reported that CD40 ligand significantly reduces the incidence of apoptotis of tumor cells in response to the chemotherapeutic agent vincristine or to serum deprivation (p. 6204). Biancone et al. described their data as suggesting that the interaction of CD40 ligand with CD40 promotes tumor growth by enhancing tumor cell invasion of tissues and tumor vascularization (p. 6207), and reported that other researchers have obtained data suggesting that the interaction of CD40 ligand with CD40 promotes the growth of malignant melanoma and renal carcinoma (p. 6201). A study by Kluth et al. (Cancer Res., 1997, 57(5):891-9, abstract attached) reported that endothelial cell expression of CD40 is ubiquitous in neovascularized areas of renal cell carcinoma, whereas endothelial CD40 is absent in tumor-free renal specimens. The study also showed that renal carcinoma cells induce endothelial cell expression of CD40 *in vitro*.

Clodi et al. (Br. J. Haematol., 1998, 103(1):217-9, copy attached) reported that CD40 ligand significantly reduces the incidence of apoptotis of CD40-bearing lymphoma cells in response to the chemotheraputic agent fludarabine, as well as the incidence of spontaneous apoptosis of the lymphoma cells (see pp. 218-219). Jakobson et al. (Int. J. Cancer, 1998, 77(6):849-53, copy attached) reported that CD40 ligand similarly protects CD40-bearing bladder carcinoma cells from apoptosis (see p. 851), and proposed a role for CD40 in tumor cell growth (p. 853). Lollini et al. (Clin. Cancer Res., 1998, 4(8):1843-9, abstract attached) reported that osteosarcoma cells and Ewing's sarcoma cells express CD40 and are stimulated

to undergo apoptosis by soluble CD40 ligand, an anti-tumor effect, but that soluble CD40 ligand also stimulates expression and secretion of matrix metalloproteinase 9, which was considered to contribute to malignancy.

It is a well established principle of patent law that in order for an invention to be unpatentable under 35 U.S.C. § 103(a), the prior art must have provided some teaching, suggestion or motivation to one of ordinary skill in the art to make the specific combination that was made by the applicant. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). At the time the invention was made, one of ordinary skill in the art would have considered the prior art to teach away from the claimed invention, by suggesting that a composition comprising the extracellular binding portion of CD40 ligand would actually stimulate tumor vascularization and growth, as described by Biancone et al. and Kluth et al., as discussed above. The prior art also suggested that the extracellular binding portion of CD40 ligand could prevent tumor cells from undergoing apoptosis, the induction of which is the basis for the anti-tumor activity of many chemotherapeutic agents, as described by Clodi et al. and Jakobsen et al. A composition comprising the extracellular binding portion of CD40 ligand might also have been expected to exert conflicting effects, on the one hand inhibiting tumor growth, and on the other promoting malignancy, as taught by Lollini et al. and discussed above.

Given that the prior art clearly taught away from the claimed invention as discussed above, one of ordinary skill in the art at the time the invention was made would not reasonably have been motivated to combine the teachings of Whitlow et al. and/or Denny et al., in view of Grabstein et al. and Armitage et al. to obtain the claimed method comprising administering to a patient a tumor-specific chimeric protein comprising the extracellular binding portion of CD40 ligand. Therefore, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as being obvious in view of the prior art is respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal

or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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